Brain Magnetic Resonance Imaging Findings in Patients With Mitochondrial Cytopathies

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Background: Mitochondrial cytopathies (MCs) are a heterogeneous group of clinical entities, some of which have classic phenotypes. Magnetic resonance imaging (MRI) has been reported to be helpful in the diagnosis of MC.

Objective: To correlate the most common brain MRI findings reported in patients with MC with the clinical findings in patients in different MC subgroups.

Design: Case series.

Setting: Patients with MCs seen at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Patients: Twenty-one patients with MC with the following phenotypes: chronic progressive external ophthalmoplegia (n=7), Kearns-Sayre syndrome (n=7), mitochondrial neurogastrointestinal encephalopathy (n=6), and myoclonic epilepsy with ragged red fiber myopathy (n=1).

Results: Brain MRI abnormalities were found in 20 (95%) of 21 patients. The most frequent abnormalities were widespread white matter hyperintensity in 19 patients (90%), supratentorial cortical atrophy in 18 patients (86%), and cerebellar atrophy in 13 patients (62%). Widespread white matter hyperintensity (P<.001) and supratentorial cortical atrophy (P=.001) were each correlated significantly with MC. Subsequent subgroup analyses showed that the absence of basal ganglia hyperintensity was correlated with Kearns-Sayre syndrome (P=.001) and the presence of supratentorial cortical atrophy was correlated with mitochondrial neurogastrointestinal encephalopathy (P=.005).

Conclusions: The presence of widespread white matter hyperintensity and/or supratentorial cortical atrophy in brain MRI may help to establish the diagnosis of MC. The radiologist has a role to play in the workup of MC by confirming the diagnosis and possibly distinguishing different subgroups of MC.

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The aim of this study was to correlate the most common brain MRI findings reported in patients with MC with the clinical findings in 4 different MC subgroups.

The 21 cases described in this report were prospectively followed up in our institution between March 1997 and February 2002. Patients were referred by the physician in charge to confirm or rule out the diagnosis, which was based on the previously reported clinical criteria.1 All cases fulfilled the following criteria: elevated serum levels of lactate, creatine kinase, and lactate dehydrogenase; elevated cerebrospinal fluid levels of lactate, lactate dehydrogenase, and proteins; and the presence of ragged red fibers in muscle biopsy specimens; and all cases had one of the following classic phenotypes: (1) chronic progressive external ophthalmoplegia (CPEO), external ophthalmoplegia combined with ragged red fibers and proximal myopathy without any other systemic manifestations12; (2) Kearns-Sayre syndrome (KSS), consisting of the classic triad of chronic external ophthalmoplegia, heart block, and pigmentary retinopathy, with cerebellar ataxia and elevated cerebrospinal fluid protein levels (>100 mg/dL) considered optional findings13; (3) mitochondrial neurogastrointestinal encephalopathy (MNGIE), comprising leukencephalopathy, chronic progressive external ophthalmoplegia, polyneuropathy, and chronic intestinal pseudo-obstruction14; and (4) myoclonic epilepsy with ragged red fiber myopathy (MERRF), consisting of myoclonic epilepsy, myoclonic ataxia, dementia, and the presence of ragged red fibers in the muscle biopsy specimen.15 Doubt persisted for 4 patients who fulfilled the above criteria, and for these patients mtDNA analysis was performed. In two of these patients we detected the presence of the entire study population. The cutoff significance level was \( \alpha = .05 \).

An initial exploration with the \( \chi^2 \) test was performed using all the variables for the studied population. For this evaluation all the different types of MC were considered a single entity. Next, using the binomial test, a subgroup analysis was performed in which the relative frequencies of the variables in each subgroup were compared with their respective frequencies in the entire study population.

In all, 28 patients with suspected MC were initially recruited. Seven were eliminated, in 4 cases because no biopsy specimen was available and in the other 3 because brain MRI was not performed. Twenty-one patients were therefore included, 12 women (57%) and 9 men (43%) (male-female ratio, 0.75:1.0) with a mean±SD age of 32.7±12.7 years. The diagnostic subgroup distribution was as follows: CPEO, n=7; KSS, n=7; MNGIE, n=6; and MERRF, n=1. Demographic and clinical characteristics are shown in Table 1. The mean period from symptom onset to brain MRI was 185.0 months (range, 16.7–393.9 months; SD, 119.8 months).

All patients except one (20/21 [95%]) had at least one abnormality on brain MRI. Two patients, one with CPEO and the other with KSS, had concomitant brain MRI abnormalities. The patient with CPEO had SCA and HPSCWM while the patient with KSS had SCA and cortical hyperintensity (Table 2). Patients in all subgroups presented with SCA, WSWH, and CbA, except for the patient with MERRF, who presented with SCA and WSWH.
The most common brain MRI abnormalities were WSWH (19/21 [90%]), SCA (18/21 [86%]), and CbA (13/21 [62%]). Widespread white matter hyperintensity was identified on T2-weighted images and FLAIR sequences, while SCA and CbA were shown on T1-weighted images, T2-weighted images, and FLAIR sequences. Using the $\chi^2$ test, WSWH (Figure 1) and SCA (Figure 2) were each correlated significantly with MC ($P=.001$ and $P=.001$, respectively) (Table 2).

On abnormal brain MRIs, subgroup analysis using the binomial test showed significant correlations between the absence of BGH (Figure 3) and KSS ($P<.001$) and between the presence of SCA (Figure 4) and MNGIE ($P=.005$). There was no significant relationship between brain MRI abnormalities and CPEO. Because only one patient had MERRF, no statistical results were available for this subgroup.

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In the present series of 21 patients, we observed 4 different mitochondrial phenotypes and their corresponding brain MRI findings. In the patients who presented with MC, WSWH, and SCA, the brain MRI findings were statistically significant. Patients with KSS exhibited a significant relationship with the absence of BGH, and in patients with MNGIE the presence of SCA was a significant brain MRI finding. The other brain MRI findings, such as SSCA, CbA, and HPSCWM, were not significantly related to any MC subgroup. In agreement with our results, Valanne et al. reported that brain MRI may be helpful in the diagnosis of classic MC, although their MRI findings were not specific.

In 6 (73%) of 8 cases, Wray et al. found brain MRI abnormalities in patients with MC who had neurologi-
cal symptoms, whereas patients with no such symptoms had either cortical atrophy or no findings on brain MRI. Sciacco et al\(^\text{10}\) confirmed that patients with full-blown neurological symptoms had various brain MRI abnormalities. According to Kapeller et al,\(^\text{11}\) the progression of neurological symptoms was associated with the spread or increased extension of these abnormalities. The most common MRI finding reported in KSS is supratentorial and infratentorial atrophy, in agreement with the results of the present study.\(^\text{24}\)

Figure 2. A 41-year-old male patient with chronic progressive external ophthalmoplegia. Axial fluid-attenuated inversion recovery magnetic resonance images show (A) parieto-occipital cortical atrophy and (B) parietotemporal cortical atrophy. The presence of supratentorial atrophy was correlated with mitochondrial cytopathy (\(P=.001\)).

Figure 3. A 37-year-old male patient with Kearns-Sayre syndrome. A, Sagittal T1-weighted magnetic resonance image shows cerebellar atrophy. B, Axial T2-weighted magnetic resonance image shows no basal ganglia hyperintensity. The absence of basal ganglia hyperintensity on brain magnetic resonance imaging was correlated with Kearns-Sayre syndrome (\(P<.001\)).
Brainstem MRI abnormalities were identified by several authors in a few cases. Kapeller et al reported abnormalities in glossopharyngeal nuclei in a patient with dysphagia, and Chu et al. reported brainstem hyperintensity in two patients. On the other hand, CbA was frequently identified in patients with KSS. These abnormalities were not found in our patients, probably because they are uncommon abnormalities. However, this disparity might be due to ethnic or geographic variations.

Our study had 3 methodological limitations. First, our population was small because the diseases studied are relatively infrequent. Second, our brain MRI data displayed great variability, probably because of the long evolution of the disease and the presence of clinical neurological symptoms in all our patients. Third, our study did not have control cases. Recent publications show that diffusion-weighted MRI and magnetic resonance spectroscopy can help in the diagnosis of MC. Oppenheim et al. reported a case of MELAS that exhibited multiple hyperintense lesions in FLAIR sequences, with a normal to slightly increased apparent diffusion coefficient. While stroke-like episodes showed both hyperintensity on T2-weighted images and an increased apparent diffusion coefficient, acute stroke showed hyperintensity on T2-weighted images and a significant reduction in apparent diffusion coefficient. A study should be carried out using apparent diffusion coefficient sequences as well as magnetic resonance spectroscopy to confirm their usefulness before their widespread application is recommended.

In the present study we found that the presence of WSWH and SCA on brain MRI may help to establish the diagnosis of MC. Kearns-Sayre syndrome was correlated significantly with the absence of BGH, and MNGIE was correlated significantly with the presence of SCA. Brain MRI has an important part to play in the workup of MC by confirming or strongly suggesting the diagnosis and by possibly identifying a subgroup of MC.

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